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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/590,316

Applicant(s)

KAMMERMEIER ET AL.

Examiner

XUE LIU

Art Unit

1791

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 July 2009.
2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 18-38 is/are pending in the application.
4a) Of the above claim(s) 34 and 38 is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 18-33 and 34-37 is/are rejected.
7) ☐ Claim(s) _____ is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB-08)
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____
Paper No(s)/Mail Date _____

DETAILED ACTION

Specification

1. Objection to the specification in the previous office is withdrawn in view of amendment to the specification.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 18-19 and 21-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmermann (US 6465226) in view of Bittner et al. (NPL document Ultrasonic atomization for spray drying: a versatile technique for the preparation of protein loaded biodegradable microspheres).

Regarding claim 18, Zimmermann teaches a process for preparing microspheres comprising an ionically crosslinked polymer, the process comprising:

(a) producing liquid aerosol droplets from a solution comprising an ionically crosslinkable polyionic polymer into a gas stream comprising compressed air and the droplets by using a nebulizing nozzle;

(b) transferring the gas stream into a gelling solution comprising bivalent or trivalent ions, whereby crosslinked polymer microspheres are formed (abstract, col. 2, lines 65 to col. 3, lines 29, col. 6, lines 38-45, col. 7, lines 28-31).

Zimmermann does not positively characterize the gas stream as continuous. However, it is obvious that the gas stream is continuous since a constant airflow is needed to separate the droplets from the nozzle (abstract, col. 3, lines 8-15).

Zimmermann does not teach using an ultrasonic nebulizer for forming the continuous gas stream.

However, Bittner et al. teach an ultrasonic atomization method for preparing microspheres by using an ultrasonic atomizer 7 connected to a stream of carrier air 6 to produce liquid aerosol droplets from a solution comprising a polymer into a continuous gas stream 8 (abstract, fig. 1, page 331, lines 1-6).

It would have been obvious to one of ordinary skill in the art at the time of the invention to provide the ultrasonic nebulizer as taught by Bittner et al. in the process of Zimmermann since Bittner et al. teach that ultrasonic nozzles have the advantage of generating droplets with a relatively uniform size distribution which could lead to more homogeneous size distribution of microspheres (page 326, lines 39-42). In addition, ultrasonic atomizers also permit easy adjustment of particle size by varying the oscillation frequency. Zimmermann does not positively characterize a separating step of the microspheres from the gelling solution. However, it is inherent that the microspheres are separated from the gelling solution since Zimmermann teaches a dwell time of 10-15 minutes of the microspheres in the precipitation bath (col. 3, lines 24-29).

Regarding claim 19, Zimmermann teaches that the ionically crosslinkable polymer is a polyanionic polymer and the gelling solution comprises a polyvalent cation (abstract, col. 4, lines 18-19, col. 6, lines 9-22 and 43-45).

Regarding claim 21, Zimmermann teaches that the ionically crosslinkable polymer is a polyanionic polymer and the gelling solution comprises di-, multi- or polyvalent cations (col. 4, lines 18-19 and col. 6, lines 38-45).

Regarding claims 22-24, Zimmermann teaches that the polyanionic polymer is alginate (abstract, col. 6, lines 9-21 and col. 7, lines 28-31), which is a salt of alginic acid.

Regarding claim 25, Zimmermann teaches that in step (a), the polyanionic polymer is present in a concentration of less than 5% by weight (col. 2, lines 56-63).

Regarding claims 26-27, Zimmermann teaches that the ion of the gelling solution is a metal cation such as Ba^{2+} and other bivalent cations (col. 6, lines 39-42).

5. Claims 20 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmermann and Bittner et al. as applied to claim 19 above, and further in view of Lim (US 4,352,883).

Regarding claim 20, Zimmermann does not teach that the polyvalent cation of the gelling solution is selected from the group consisting of poly (allylamine hydrochloride), poly (ethylene imine), poly (diallyldimethylammonium chloride), polyamide-polyamine-epichlorhydrine, chitosan, amino-dextran, and protamine sulfate.

However, Lim teaches that the polyvalent cation of the gelling solution is polyethylencimine (col. 7, lines 59-64).

It would have been obvious to one of ordinary skill in the art at the time of the invention to select polyethyleneimine as the polyvalent cation in the gelling solution in the method of Zimmermann since Lim teaches that polysaccharide can be (a) gelled to form a shape retaining

mass by being exposed to a change in conditions such a pH change or by being exposed to multivalent cations such as Ca^{++} ; and (b) permanently “crosslinked” or hardened by polymers containing reactive groups such as amine or imine groups which can react with acidic polysaccharide constituents (col. 2, lines 37-46).

Regarding claim 28, Zimmermann teaches that the ion of the gelling solution is a metal cation such as Ba^{2+} and other bivalent cations.

Zimmermann does not positively teach that the metal cation of the gelling solution is Ca^{2+} .

However, Lim teaches that Ca^{2+} is used as the metal cation of the gelling solution (col. 2, lines 37-42).

It would have been obvious to one of ordinary skill in the art at the time of the invention to select Ca^{2+} as the metal cation of the gelling solution in the method of Zimmermann since Lim teaches that Ca^{2+} is a multivalent cation which forms crosslinked polymer microspheres with polysaccharide (col. 2, lines 37-42). The Ca cation is viewed as functional equivalent, providing gel.

6. Claims 29-30, 32 and 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmermann in view of Bittner et al. as applied to claim 18 above, and further in view of Andersson et al. (WO 03/091315).

Regarding claims 29-30 and 36, Zimmermann does not teach that the gelling solution additionally comprises a surfactant present in an amount of from 0.05 to .15% by weight.

However, Andersson et al. teach that droplets which form polysaccharide beads are collected in a bath comprised of a liquid having a reduced surface tension by adding a surfactant to the liquid (page 7, line25- page 8, line 1).

It would have been obvious to one of ordinary skill in the art at the time of the invention to incorporate the teaching of Andersson et al. in the method of Zimmermann to provide a surfactant in the gelling solution to facilitate movement of the beads in the solution.

Andersson et al. do not positively teach the amount of surfactant that is added, however, it would have been obvious to one of ordinary skill in the art to select an appropriate amount of surfactant to satisfactorily lower the surface tension of the solution. Additionally the amount of surfactant is known to affect particle size of the capsules.

Regarding claim 32 and 37, Zimmerman does not positively teach that the temperature of the solution of the ionically crosslinkable polyionic polymer according to step (a) is kept within a temperature of from 25 to 35 deg C. However, Andersson et al. teach the temperature of the polysaccharide solution should be kept low, such as below about 40 deg C (page 5, lines 2-4). It would have been obvious to one of ordinary skill in the art at the time of the invention to incorporate the teaching of Andersson et al. in the method of Zimmermann since Andersson et al. teach that keeping the solution at a low temperature avoids formation of lumps (page 5, lines 2-4).

Regarding claim 35, Zimmerman does not teach filtering the microspheres through a screen.

However, Andersson et al. teach filtering the beads to a sieve 14 for particle concentration (page 13, line 5 and fig. 1).

It would have been obvious to one of ordinary skill in the art at the time of the invention to provide the filtering step as taught by Andersson et al. in the method of Zimmermann in order to obtain microspheres with a more uniform size distribution.

7. Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmerman in view of Bittner et al. and Andersson et al. as applied to claim 29 above, and further in view of Lemoine et al. NPL document Preparation and characterization of alginate microspheres containing a model antigen).

Regarding claim 31, Andersson et al. do not positively teach that the surfactant is selected from the group consisting of polyoxyethylene sorbitans and surfactants comprising a block copolymer of ethylene oxide and/or propylene oxide.

However, Lemoine et al. teach the use of polyoxyethylene sorbitan trioleate as surfactant in the production of alginate microspheres (see section 2.1).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use polyoxyethylene sorbitan trioleate as surfactant in the method of Zimmermann since Lemoine et al. teach that polyoxyethylene sorbitan trioleate, or Tween 85 produced less heterogeneous and smaller microspheres (table 1 and section 3.1). Surfactant of Lemoine is viewed as functional equivalent.

8. Claim 33 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmermann in view of Bittner et al. as applied to claim 21 above, and further in view of Vasington et al. (US

5,387,522), Andersson et al. (WO 03/091315) and Lemoine et al. NPL document Preparation and characterization of alginate microspheres containing a model antigen).

Regarding claim 33, Zimmermann teaches that in step (a), the solution comprises about 2 % by weight sodium alginate (col. 2, lines 56-63). Zimmermann does not teach that the solution comprises of from 0.75% to 1.5% by weight of sodium alginate. Zimmermann does not positively teach that the sodium alginate is low viscosity.

However, Vasington et al. teach low viscosity sodium alginates that are used as the polyanionic polymer. Further, Vasington et al. teach that the concentration of the sodium alginates in the mixture should range from about 0.5 to about 1.4%, preferably about 0.6 to 1.2%, most preferably about 0.7-0.9% (col. 5, lines 17-51).

It would have been obvious to one of ordinary skill in the art at the time of the invention to incorporate the teaching of Vasington et al. in the method of Zimmerman et al. since Vasington et al. teach that low percentage of sodium alginate result in higher porosity of the gel beads to nutrients and other factors (col. 5, line 46-51). Moreover, lowering the viscosity of sodium alginates produces smaller microspheres. Zimmermann teaches that the ion of the gelling solution is a metal cation such as Ba^{2+} and other bivalent cations. Zimmermann does not positively teach that the metal cation of the gelling solution is Ca^{2+} . However, Vasington et al. teach that the cation in the gelling solution is Ca^{2+} (col. 6, lines 46-48, col. 7, lines 28-32 and col. 8, lines 42-47).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use Ca^{2+} as the cation in the gelling solution as taught by Vasington et al. since Vasington et

al. teach that Ca^{2+} forms stable calcium alginate gel containing entrapped cells (col. 8, lines 42-47).

Zimmermann does not teach that the gelling solution additionally comprises a surfactant present in an amount of from 0.05 to .15% by weight.

However, Andersson et al. teach that droplets which form polysaccharide beads are collected in a bath comprised of a liquid having a reduced surface tension by adding a surfactant to the liquid (page 7, line 25- page 8, line 1).

It would have been obvious to one of ordinary skill in the art at the time of the invention to incorporate the teaching of Andersson et al. in the method of Zimmermann to provide a surfactant in the gelling solution to facilitate movement of the beads in the solution.

Andersson et al. do not positively teach the amount of surfactant that is added, however, it would have been obvious to one of ordinary skill in the art to select an appropriate amount of surfactant to satisfactorily lower the surface tension of the solution. Andersson et al. do not positively teach that the surfactant is poly (oxyethylene) 20-sorbitane monolaurate.

However, Lemoine et al. teach the use of polyoxyethylene sorbitan trioleate as surfactant in the production of alginate microspheres (see section 2.1).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use polyoxyethylene sorbitan trioleate as surfactant in the method of Zimmermann since Lemoine et al. teach that polyoxyethylene sorbitan trioleate, or Tween 85 produced less heterogeneous and smaller microspheres (table 1 and section 3.1).

While Andersson et al. teach the use of polyoxyethylene sorbitan trioleate, as opposed to poly (oxyethylene) 20-sorbitane monolaurate as recited in claim 33.

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute polyoxyethylene sorbitan trioleate with poly (oxyethylene) 20-sorbitane monolaureate since both surfactants are structurally similar.

Response to Arguments

9. Applicant's arguments filed 7/1/09 have been fully considered but they are not persuasive. Applicant argues that one of ordinary skill in the art would not have modified the process of Zimmermann by the teachings of Bittner because such a modification is contrary to the teachings of Zimmermann as Zimmermann discloses that the central idea of Zimmermann's process is to use a spray nozzle with two channels, not ultrasonic atomization. However, motivation to modify the primary reference is not necessarily required in the primary reference itself. The fact that there is no motivation to modify the invention of Zimmermann with ultrasonic atomizers in the disclosure of Zimmermann does not constitute teaching away from the use of ultrasonic atomization, provided the secondary reference Bittner already provides the cited benefit of uniform size distribution of microspheres by using ultrasonic atomizers (see page 326, ll. 39-42).

10. Applicant argues that the teaching of Bittner are not compatible with those of Zimmermann since the modification would require a complete re-design of the spray nozzle construction disclosed by Zimmermann. However, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the

references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). Furthermore, the claims are directed to a process; therefore, it is irrelevant whether the structure of Bittner may be bodily incorporated into the structure of Zimmermann.

11. Applicant further argues that Zimmermann teaches a pressure of 40 mbar to produce droplets with a size of 100-300 microns rather than spray droplets that typically have a size of 10-20 microns. However, it is noted that the features upon which applicant relies (i.e., the particular size of the droplets formed by the process) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The claim recites a process for forming microspheres but does not specify the size of the microspheres. Since Zimmermann teaches a process of forming **microcapsules** having a maximum diameter of 300 micrometers (see abstract), the claim limitation is met by Zimmermann.

Conclusion

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to XUE LIU whose telephone number is (571)270-5522. The examiner can normally be reached on Monday to Friday 9:30 - 6:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Katarzyna Wyrozebski can be reached on (571)272-1127. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/KAT WYROZEBSKI/
Supervisory Patent Examiner, Art Unit 1791

/X. L./
Examiner, Art Unit 1791